# CONTINUOUS KRAPCHO DEALKOXYCARBONYLATION IN API SYNTHESIS

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## ABSTRACT

*A high pressure and high temperature continuous flow reactor has been used to intensify a Krapcho dealkoxycarbonylation reaction in the context of API synthesis. The reactor enables operation of the reaction above temperatures possible in batch and thus significantly increased conversion rates are achieved. Also a broader choice of solvents is possible by the use of the continuous process. Batch and continuous reaction are compared in terms of operation range and space-time-yield. Despite lower concentrations of the reactants in the continuous process, space-time-yield exceeds that of the batch process by more than an order of magnitude due to the higher reaction rates.*

*Keywords: Flow synthesis, process intensification, Krapcho dealkoxycarbonylation*

## INTRODUCTION

The method of Krapcho is a simple procedure for the selective dealkoxycarbonylation of molecules under neutral conditions [1,2]. It involves heating of the respective reactant molecule in an aprotic polar solvent with added water and sometimes salts. At ambient pressure, the choice of solvent is limited to high boiling polar aprotic solvents such as DMF and DMSO due to the demanding temperatures. Figure 1 displays reaction temperature and time for several Krapcho reactions reported in literature [3,4].

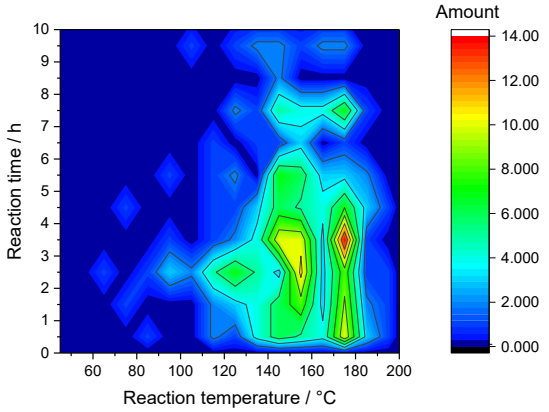


***Figure 1: Overview over reaction conditions for different Krapcho reactions reported in literature, $n_{total}$ = 364 [3,4]***

Obviously, the majority of these reactions only progresses at temperatures well above 140 °C, still requiring reaction times of several hours. In order to intensify the reaction beyond the original batch protocol, a continuous high pressure and high temperature flow reactor is utilized to access reaction temperature windows not possible in batch. By pressurizing the reactor, also alternative low boiling solvents could be employed, benefiting from their high volatility for easier workup. The continuous reactor is tested for a typical Krapcho reaction with pharmaceutical relevance, namely the synthesis of 3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**DHBD** [5], Figure 2. **DHBD** and its derivatives are important precursor molecules for the synthesis of substituted paullones and paullone derivatives, a class of protein kinase inhibitors and anti-cancer agents [6–8].

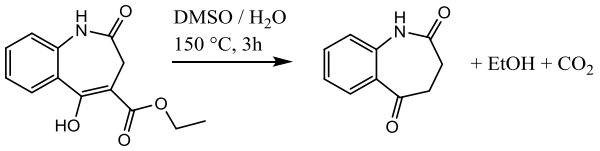


***Figure 2: Krapcho dealkoxycarbonylation for the synthesis of DHBD in batch mode***

## RESEARCH CONCEPT

In order to examine the reaction in detail, a continuous high pressure and high temperature flow reactor has been designed and characterized [9].

As shown in Figure 3, the center piece of the setup is a stainless steel coil reactor with dimensions $d_i$ x L = 1.016 x 2,500 mm, $V_R$ = 2.027 mL, which is submerged in and heated by an oil bath. The reactor is fed by a HPLC pump and kept at a constant pressure of 37.5 bar to prevent boiling of the solvent. At a given flow rate, 500 µL of the reactant solution are loaded in the sample loop and injected into the inlet stream.

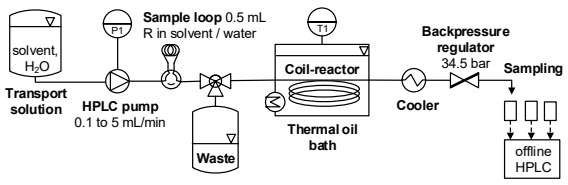


***Figure 3: Setup of the continuous flow reactor used to study the Krapcho reaction***

The reactor outlet stream is collected and analyzed via HPLC. In order to generate conversion-time-profiles



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this procedure is repeated for various combinations of temperature (160 – 200 °C) and flow rate (0.1 – 2 mL $min^{-1}$). For comparison batch reactions are performed in a Mettler Toledo EasyMax 102 synthesis workstation.

**Kinetic analysis**

The conversion-time-profile of the reactant $X_R$ can be described by a pseudo 1st order kinetic equation, where $t_R$ is the residence time of sample fluid element in the heated zone of the continuous reactor [10]:

$$X_R = 1 - exp(-k \cdot t_R) \quad (1)$$

Since residence time distribution in the coil reactor is found to closely follow plug flow behavior [9], residence time $t_R$ is calculated via reactor volume $V_R$ and volumetric flow rate $\dot{V}$, corrected by the expansion of the fluid upon heating:

$$t_R = \frac{V_R}{\dot{V}} \frac{\rho_{S,T}}{\rho_{S,25°C}} \quad (2)$$

By fitting equation (1) to experimentally determined conversion-over-time data, rate constants $k$ can be determined. By employing Arrhenius´ law, activation energy $E_A$ and frequency factor $k_0$ may be calculated:

$$k(T) = k_0 \cdot exp(-E_A/(R \cdot T)) \quad (3)$$

Combination of equations (1) – (3) results in an expression for the conversion in the continuous reactor as function of temperature and flow rate [9]:

$$X_R(T, \dot{V}) = 1 - exp\left[-k_0 \cdot e^{-\frac{E_A}{RT}} \cdot \frac{V_R}{\dot{V}} \frac{\rho_{S,T}}{\rho_{S,25°C}}\right] \quad (4)$$

## RESULTS AND DISCUSSION

**Reaction characterization**

Since water is added as reactant, the influence of its concentration on reaction rate was examined.

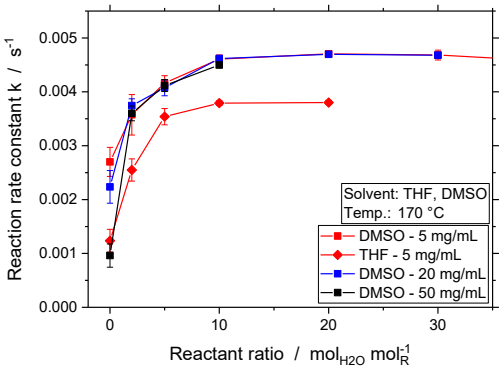


***Figure 4: Influence of the ratio of water and reactant on the rate of the dealkoxycarbonylation***

Figure 4 displays reaction rate constants for different ratios of added water to reactant concentration at varied reactant concentrations in solvents DMSO and THF. In general, rate constants increase with the amount of water added per reactant, until a maximum $k$-value is reached at a ratio of about 10. This behavior can be observed for different reactant concentrations ranging from 5 to 50 mg $mL^{-1}$ in DMSO.

For no added water, the reaction still takes place. This might be due to the hygroscopic nature of DMSO, which always contains small amounts of water. For low ratios of added water to reactant concentration, error bars are significantly larger, indicating a lower accuracy of the used 1st order fit. In this regime, the reaction behaves more like a 2nd order reaction where water concentration becomes limiting. For THF as solvent, a similar behavior is observed, however, the maximum value of $k$ is significantly lower than that observed in DMSO.

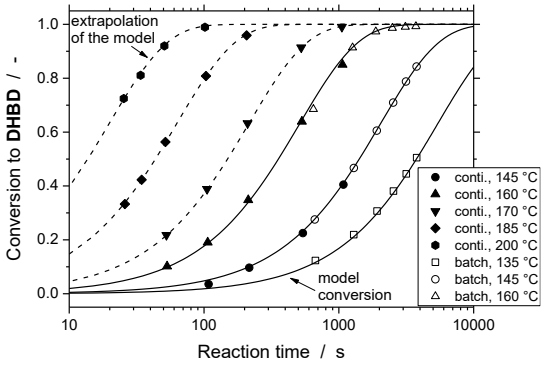


***Figure 5: Conversion profiles at different temperatures in DMSO in batch and continuous mode [9]***

Figure 5 displays typical conversion-time profiles of **R** to **DHBD** in DMSO for different temperatures in the batch and continuous reactor. Conversion profiles were also modeled using equation (4) and batch data to fit the parameters. Dotted curves represent extrapolations of that model to higher temperatures, with parameters extracted from reactions ≤ 160 °C.

Batch and continuous conversions are in very good agreement, however, the reaction temperature in batch is limited. Employing the continuous reactor, temperatures of up to 200 °C can be realized resulting in a significantly intensified reaction. Consequently, shorter reaction times are sufficient to reach complete conversion (~ 3 min vs. ~ 3 h respectively).

**Solvent selection**

To identify an optimal solvent for the Krapcho reaction, different solvents have been examined as reaction medium. Figure 6 summarizes the derived rate constants at different temperatures. Whilst aprotic-polar solvents show significant reaction rates, ethanol and i-propanol are not suited as reaction medium. Here, the equilibrium between the reactant and a carboxylate intermediate might be affected negatively. Considering aprotic-polar solvents, rate constants do not differ dramatically. However, DMSO and acetone show the highest rate



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constants while values of propylene carbonate (PC) and ethyl acetate (EA) are about 25 % lower.

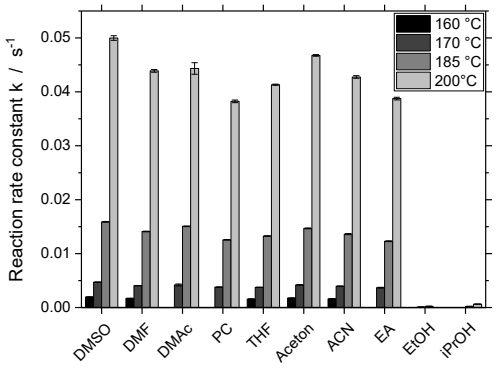


***Figure 6: Reaction rate constants k in different solvents***

Besides reaction rate, reactant solubility in the respective solvent is an important property. Solubility curves of **R** in different solvents, measured via HPLC from a saturated solution, for n ≥ 3 samples each, are given in Figure 7. Only DMSO, DMF and DMAc exhibit high solubility for the reactant **R** while acetone, PC, EA and ACN show unsatisfactory solubility especially at room temperature. Taking a combined look at reaction rate and solubility, it becomes apparent that DMSO, DMAc and DMF are the most promising solvent candidates, since they show both, relatively high rate constants and good solubility. THF is the best of the low boiling solvents. While the solubility for the reactant is not as high as in DMSO for example, it still exceeds the other low boiling solvents by a factor ~ 3.

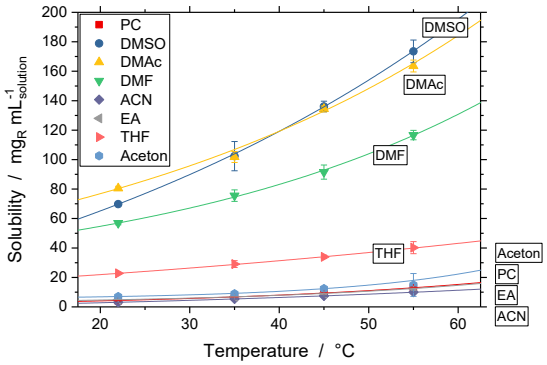


***Figure 7: Solubility curves of the reactant R in different aprotic-polar solvents, n ≥ 3***

### Comparison of batch and continuous process

To assess the process modes, it is interesting to consider the operation range of the respective process and compare the space-time-yield (STY) as a measure of process performance.

Operation ranges, given in Figure 8, can be interpreted as follows: In the batch process, solubility is not an issue since dissolution of the reactant can take place during heating of the mixture and at reaction temperature, solubility is high anyway. In contrast, in continuous mode, the reactant has to be dissolved prior to pumping to prevent reactor clogging and pump damage by un-dissolved solids, so reactant concentration is limited. In the batch process reaction temperature is limited by the boiling temperature of the reaction mixture. Since water is added proportional to the reactant concentration, maximum possible reaction temperature is decreasing with increasing reactant concentration (see Figure 8). In the pressurized continuous reactor, this is not an issue and higher reaction temperatures can be reached.

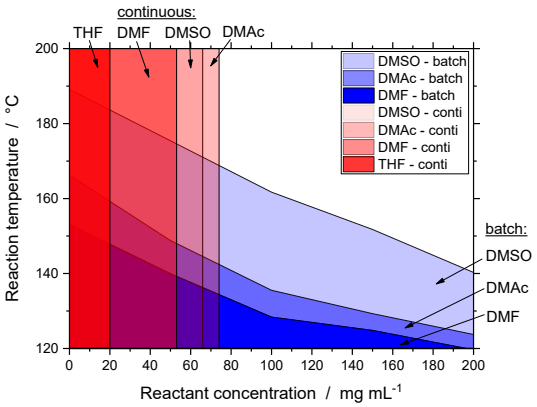


***Figure 8: Operation range of the batch and the continuous process***

To quantitatively the influence of reaction temperature and concentration on the performance of both processes, *STY* is theoretically assessed as follows: For the batch, *STY* depends on the chosen reactant concentration $c_R$ and the resulting processing time $t_{proc}$ which is a function of the reaction temperature und ultimately of the reactant concentration due to added water as stated above:

$$STY_b = \frac{c_R}{t_{proc.}(c_R)} \cdot M_{DHBD}/M_R \qquad (5)$$

For the continuous process, *STY* follows from the maximum solubility of the reactant $S_R$ and the volumetric flow rate necessary to provide a sufficient reaction time for a conversion of 99.9 %:

$$STY_c = S_R(T_S) \cdot \frac{\dot{V}_{X=99.9\%}(T_R)}{V_R} \cdot M_{DHBD}/M_R \qquad (6)$$

The calculated *STY* are displayed in Figure 9, where values for batch represent the highest *STY* possible at the optimum reactant concentration and temperature while the values for the continuous process are calculated for dissolution temperature $T_S$ = 25 °C and reaction temperature $T_R$ = 200 °C.

It can be concluded that the *STY* possible in the batch process is about an order of magnitude smaller than in the continuous process for the high boiling solvents. This can be contributed to the low temperatures and therefore slow reaction in batch. This effect can be seen especially for THF where the low boiling point would lead to reaction times of several years. Although reactant



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concentration is higher in the batch process, this advantage does not balance out the slow rates. In continuous mode, due to the fast reaction, DMF, DMSO and DMAc show the highest *STY* of around 10 – 20 mg $mL^{-1}_{reactor}$ $min^{-1}$.

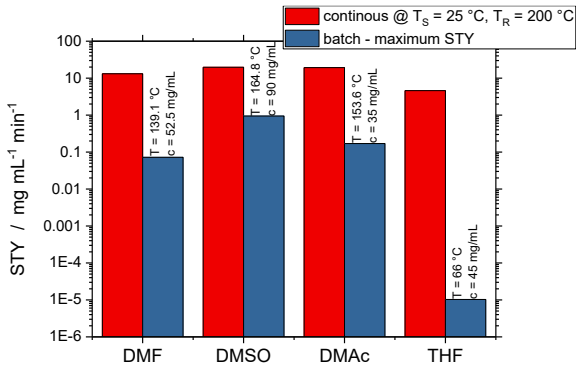


***Figure 9: Calculated STY for the batch and continuous process in logarithmic scaling***

In conclusion, the superior performance of the continuous process can mainly be attributed to the possibility to operate at high temperatures. Although similar temperatures could also be reached in a sealed or pressurized batch reactor, the distinct advantage of a high surface to volume ratio and therefore excellent heat transfer properties of the continuous reactor would still lead to an advantage over a pressurized batch reactor. The batch reactor would need longer heating and cooling times and therefore an overall longer processing time rendering the fast reaction times useless. In addition, higher safety properties usually attributed to continuous systems and low cost for the commonly available materials are distinct advantages of the continuous process.

## CONCLUSIONS

In this contribution, a continuous process for the intensification of the Krapcho dealkoxycarbonylation reaction is established and the synthesis of the pharmaceutically relevant molecule DHBD is studied as model process in detail. To assess the performance of the continuous reactor it is compared to the original batch process.

It was found that the dealkoxycarbonylation can be significantly intensified in the continuous reactor due to the high reaction temperatures possible, resulting in a reaction time reduction from 3 h in batch to < 3 min in the continuous reactor. Exploiting the pressurized reaction conditions in the continuous reactor, the choice of solvent can be broadened significantly. It was found, that all aprotic-polar solvents under investigation are principally suited as reaction medium since similar rates were measured. However, due to the higher solubility DMSO, DMF and DMAc are preferred.

Compared to the batch process, *STY* in the continuous reactor is one to two orders of magnitude higher when operated under higher temperatures that cannot be realized in the batch reactor due to boiling of the reactant mixture.

## ACKNOWLEDGEMENT

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## NOMENCLATURE

| | | |
|---|---|---|
| $c_R$ | [mmol $mL^{-1}$] | reactant concentration |
| $d_i$ | [mm] | inner diameter |
| $E_A$ | [J $mol^{-1}$] | activation energy |
| k | [$s^{-1}$] | reaction rate constant |
| $k_0$ | [$s^{-1}$] | frequency factor |
| L | [m] | length of the coil-reactor |
| M | [g $mol^{-1}$] | molar mass |
| R | [J $K^{-1}$ $mol^{-1}$] | universal gas constant |
| $\rho_S$ | [g $mL^{-1}$] | solvent density |
| S | [mg $mL^{-1}$] | solubility |
| STY | [mg $mL^{-1}$ $min^{-1}$] | space time yield |
| T | [°C], [K] | temperature |
| $V_R$ | [mL] | reactor volume |
| $\dot{V}$ | [mL $min^{-1}$] | volumetric flow rate |
| $X_R$ | [-] | reactant conversion |

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